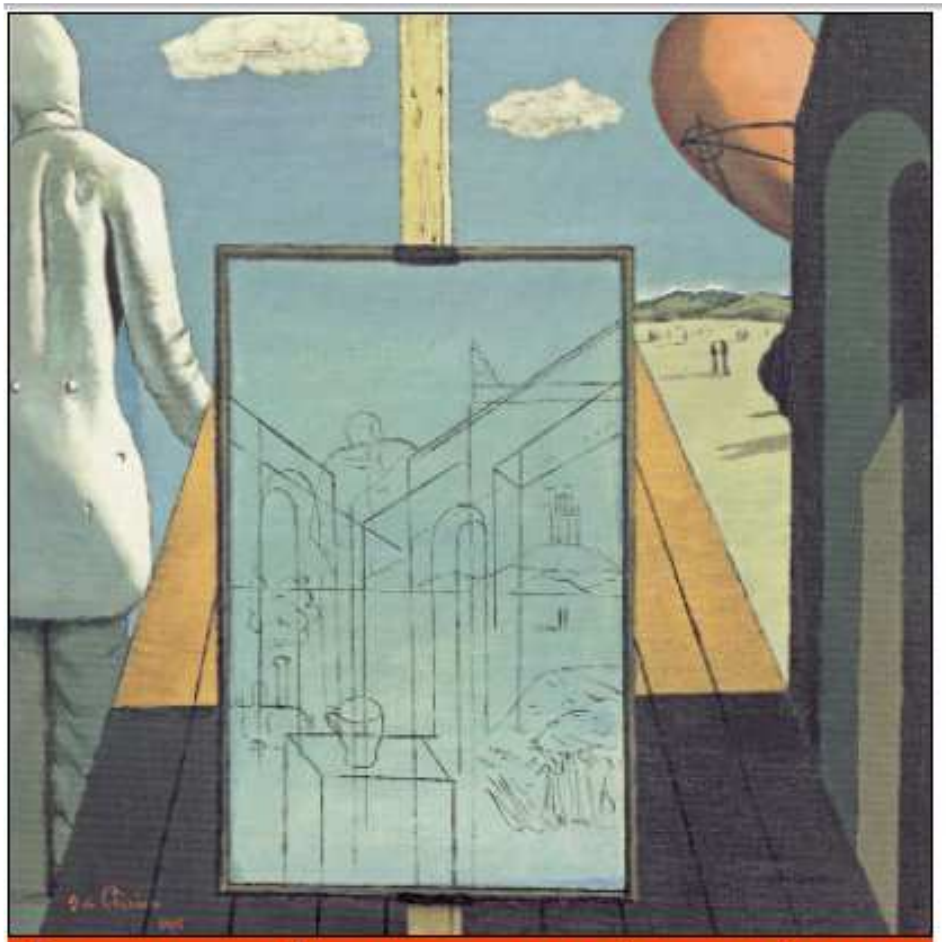


La consulenza genetica e i test genetici nella pratica clinica

Indicazioni, percorsi e interpretazioni

Siena, 24 settembre 2009

LA CONSULENZA GENETICA E I TEST GENETICI NELLE MALATTIE RENALI

9.00 - *La sindrome di Alport*

Francesca Mari, Genetica Medica, AOUS

Sindrome di Alport (ATS)
nefropatia ereditaria progressiva
eterogenea dal punto vista clinico e genetico

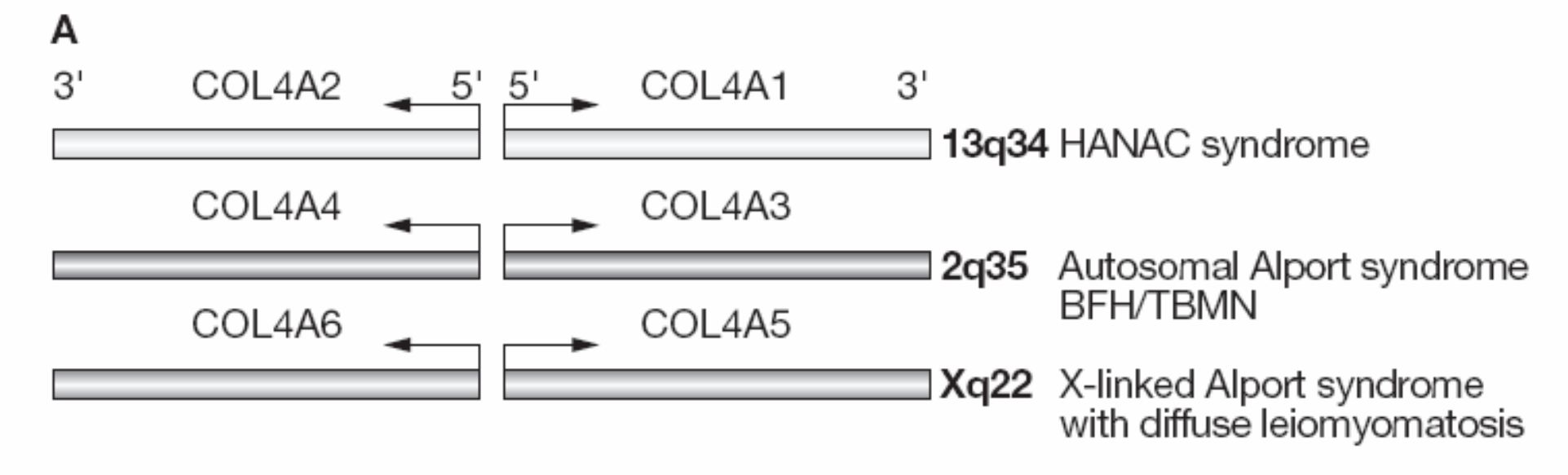
CRITERI CLINICI

- Storia familiare positiva per ematuria o insufficienza renale cronica (IRC)
- Alterazioni ultrastrutturali della membrana basale glomerulare (GMB)
- Ipoacusia neurosensoriale per le alte frequenze
- Anomalie oculari (lenticono, macchie perimaculari, erosioni corneali ricorrenti)

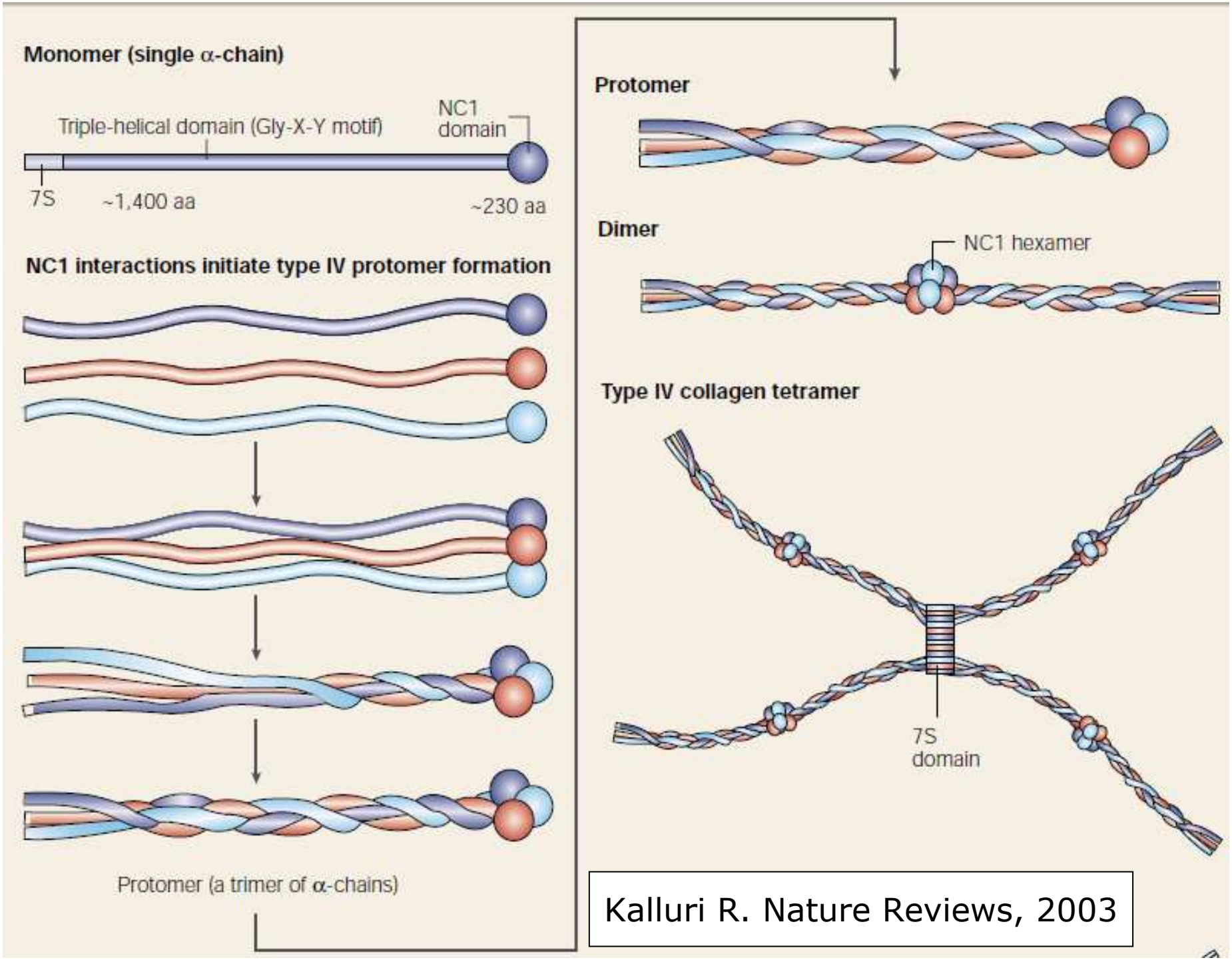
0.3-2.6% pazienti che sviluppano ESRD in Europa

Sindrome di Alport (ATS)-malattia delle membrane basali (del collagene di tipo IV)

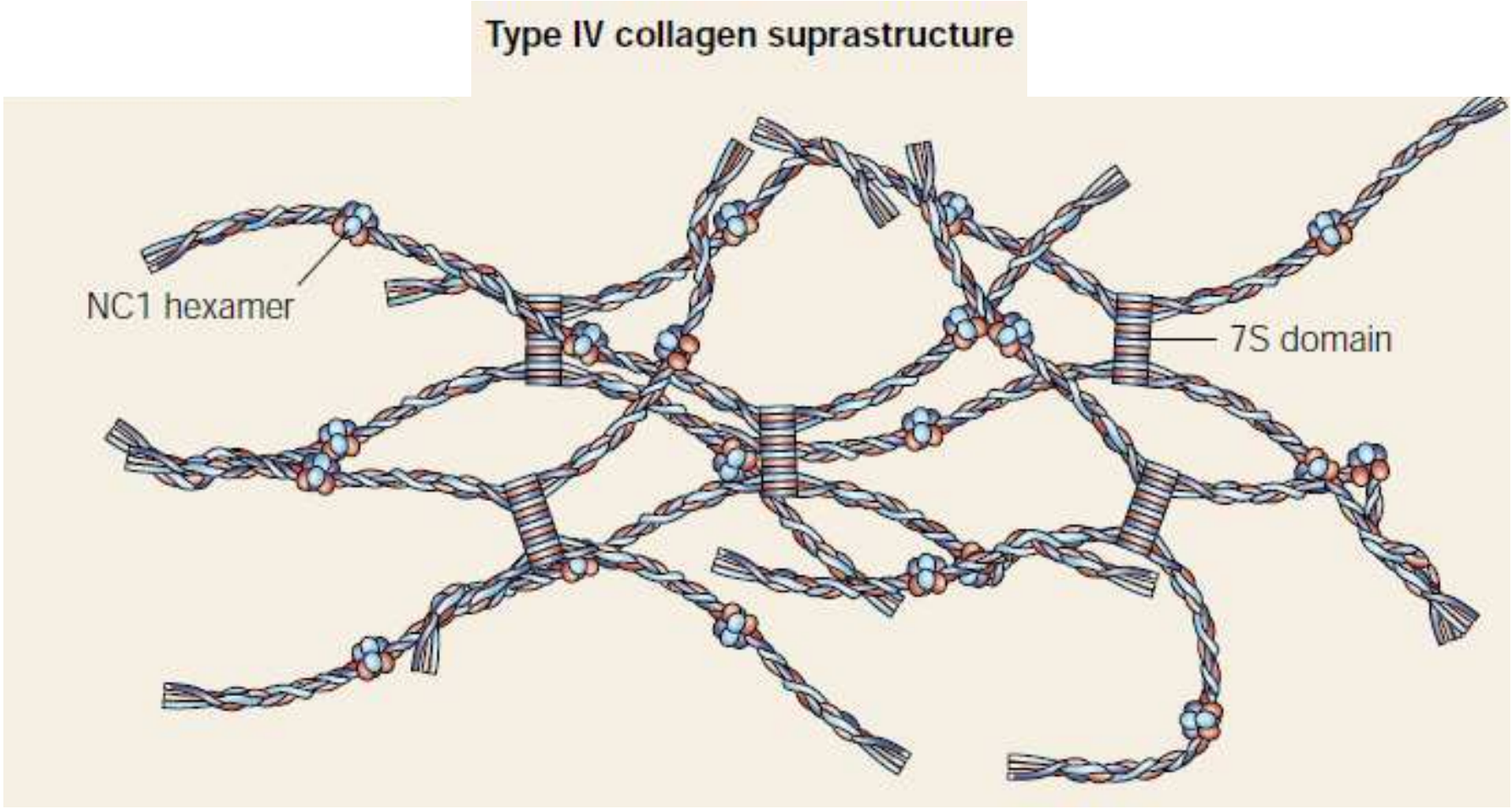
- X-legata (circa il 90% dei casi) – gene COL4A5
- autosomica recessiva – geni COL4A3 e COL4A4
- autosomica dominante – geni COL4A3 e COL4A4



Gubler MC (2008) Inherited diseases of the glomerular basement membrane
Nat Clin Pract Nephrol **4:** 24–37, 2007



Kalluri R. Nature Reviews, 2003



Kalluri R. Nature Reviews, 2003

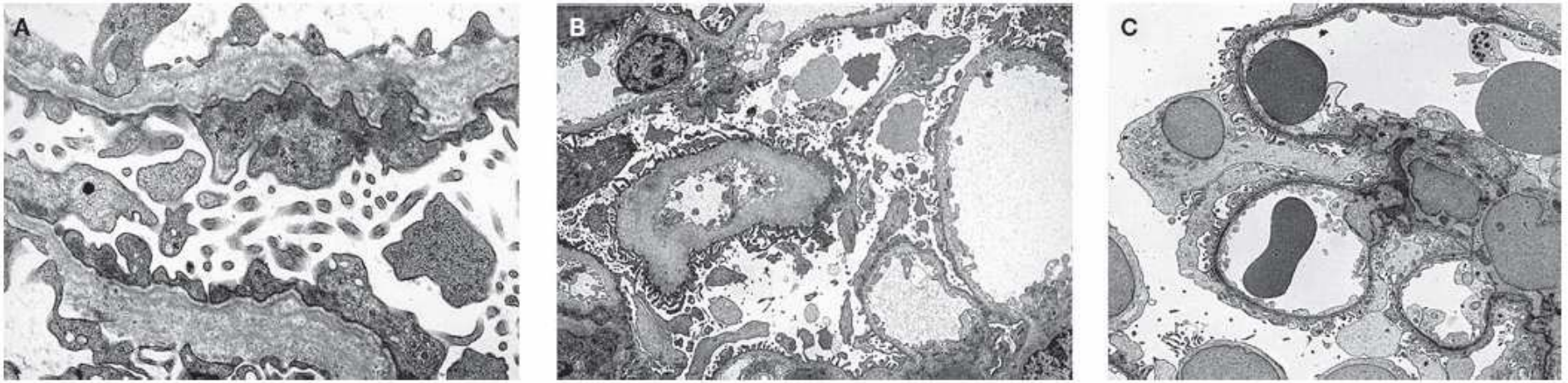


Figure 3 Electron microscopy images of renal tissue from patients with Alport syndrome. (**A**) Thickening and splitting of the glomerular basement membrane (GBM) in an 11-year-old patient. The inner and outer contours of the GBM are 'festooned'. Magnification ×30,000. (**B**) In tissue from a 12-year-old patient observed under low magnification, the irregular thickness of the GBM is evident. Magnification ×5,400. (**C**) Diffuse thinning of the GBM in a 3-year-old male patient. Magnification ×6,200. All sections stained with uranyl acetate and lead citrate.

Gubler MC (2008) Inherited diseases of the glomerular basement membrane
Nat Clin Pract Nephrol **4:** 24–37, 2007

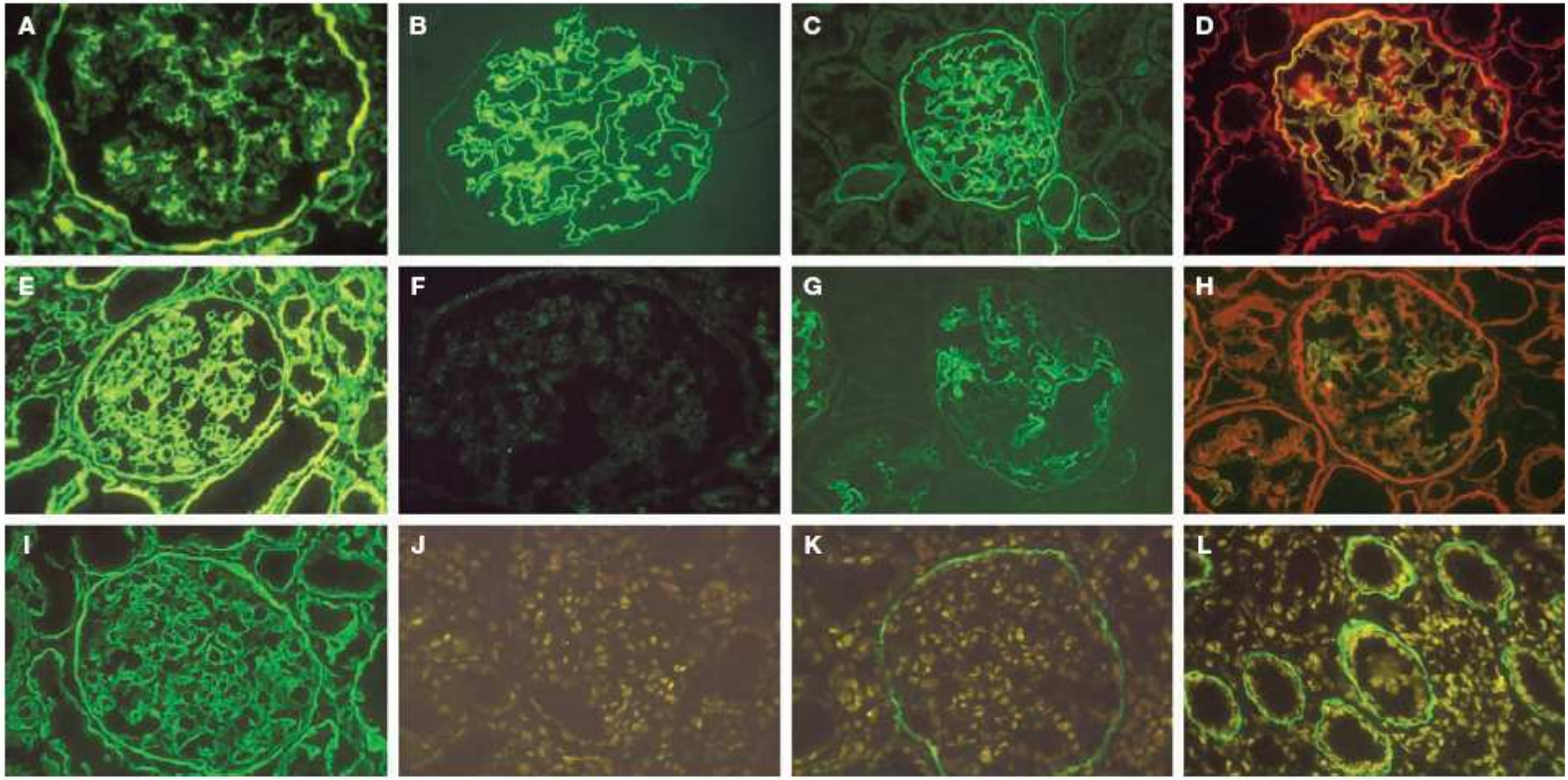
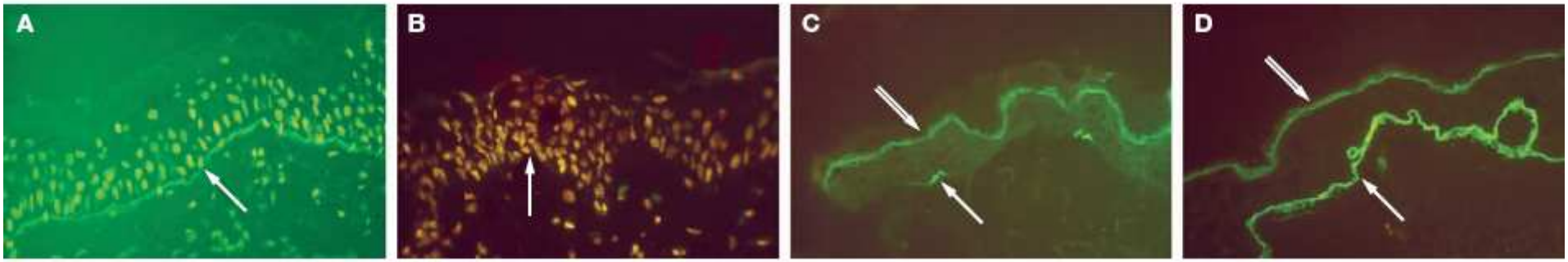


Figure 4 Immunohistological analysis of the renal distribution of type IV collagen chains. The analysis was carried out in (**A–D**) control, X-linked (**E**,**F**) male and (**G**,**H**) female Alport syndrome patients, and (**I–L**) patients with autosomal recessive Alport syndrome, using antibodies to α1(IV) (A,E,I), α3(IV) (B,F,J), or α5(IV) (C,G,K,L) chains. Double labeling was made with anti-α2(IV) in red, and anti-α5(IV) in green (D,H). In control kidney, the α1(IV) chain is present in the mesangial matrix, Bowman's capsule, and the extraglomerular basement membranes (A). The α3(IV) and α5(IV) chains are distributed within the GBM (B and C, respectively). The Bowman's capsule is strongly α5(IV)-positive (C). In X-linked Alport syndrome, no α3(IV) expression was detected in a male patient (id for α4–α5) (F), whereas the distribution is segmental in a female patient (G). In autosomal recessive Alport syndrome, no α3(IV)–α5(IV) labeling is detected in the GBM (J) whereas α5(IV) is expressed in Bowman's capsule (K) and the basement membranes of the collecting ducts (L). In both types of Alport syndrome, α1(IV) is diffusely expressed in the GBM (E,I). Abbreviation: GBM, glomerular basement membrane.

Gubler MC (2008) Inherited diseases of the glomerular basement membrane
Nat Clin Pract Nephrol **4:** 24–37, 2007

Figure 5 Immunohistological analysis of the distribution of the α5(IV) collagen chain

controllo Maschio ATS XL Femmina ATS XL ATS AR



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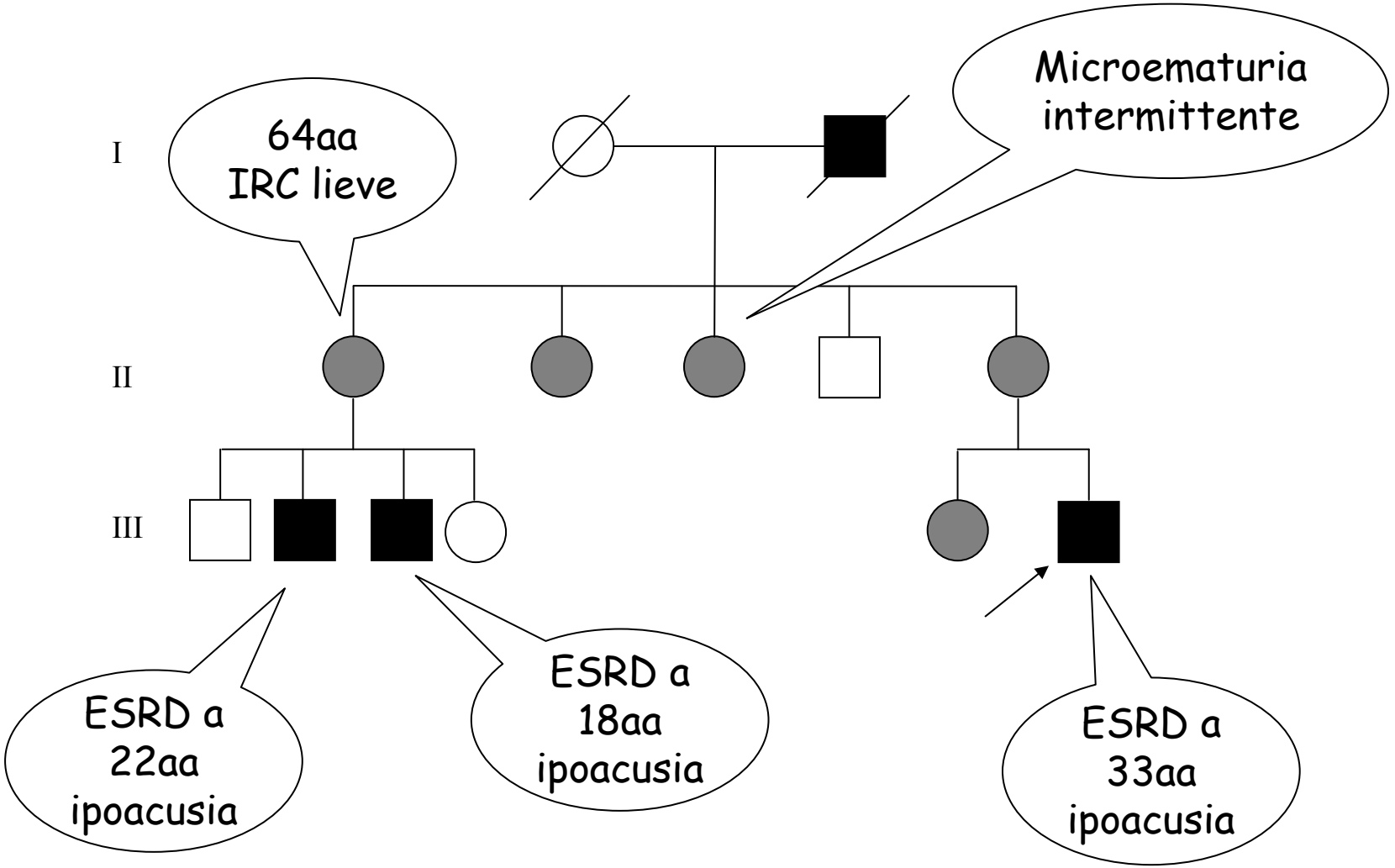

I
II
III
64aa
IRC lieve
Microematuria
intermittente
ESRD a
22aa
ipoacusia
ESRD a
18aa
ipoacusia
ESRD a
33aa
ipoacusia

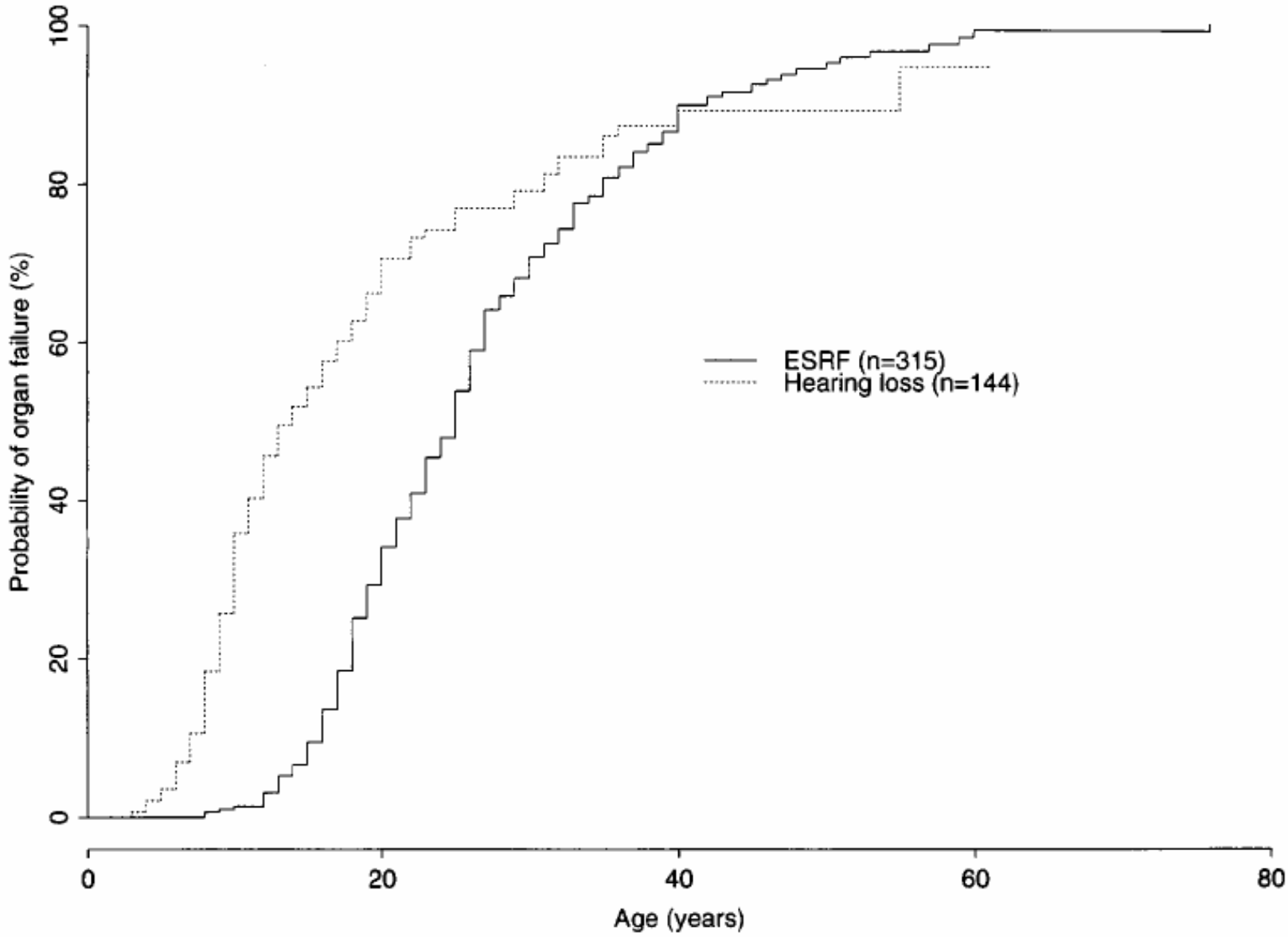
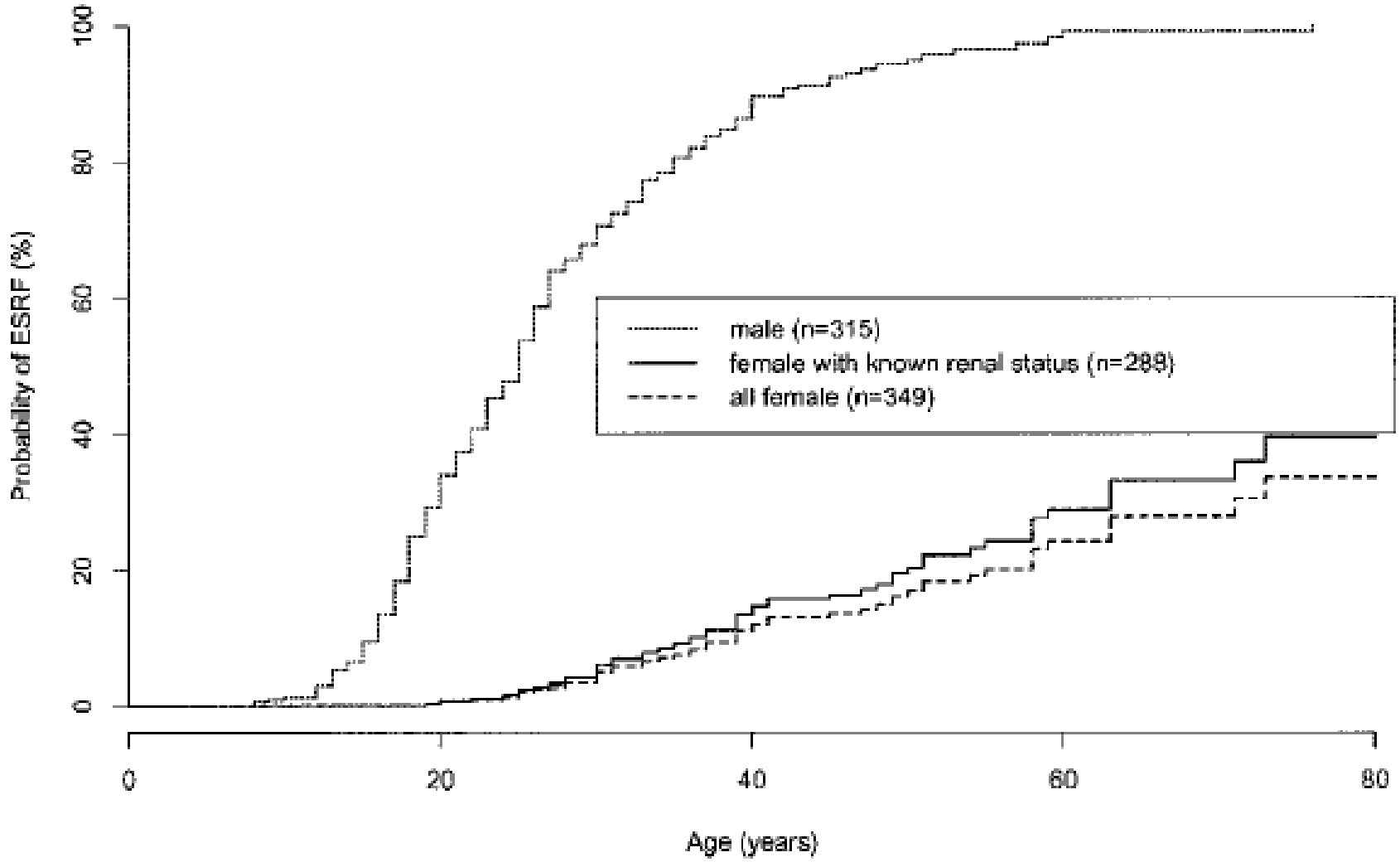
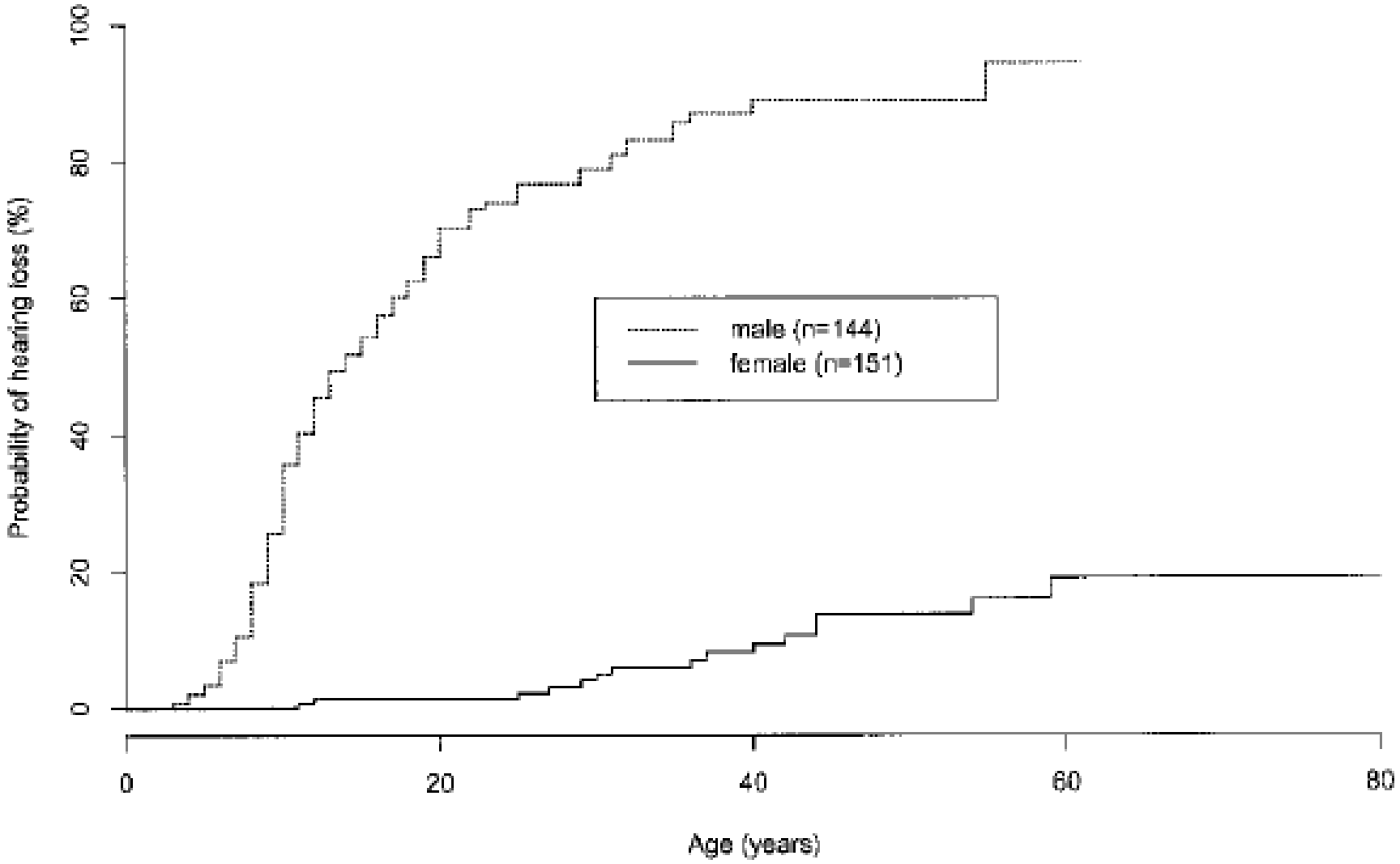


Figure 1. Probability of end-stage renal disease (ESRD) or hearing loss in male patients with COL4A5 mutation. Precise chronological data for evolution of renal and auditory functions were obtained in 315 and 144 patients, respectively.

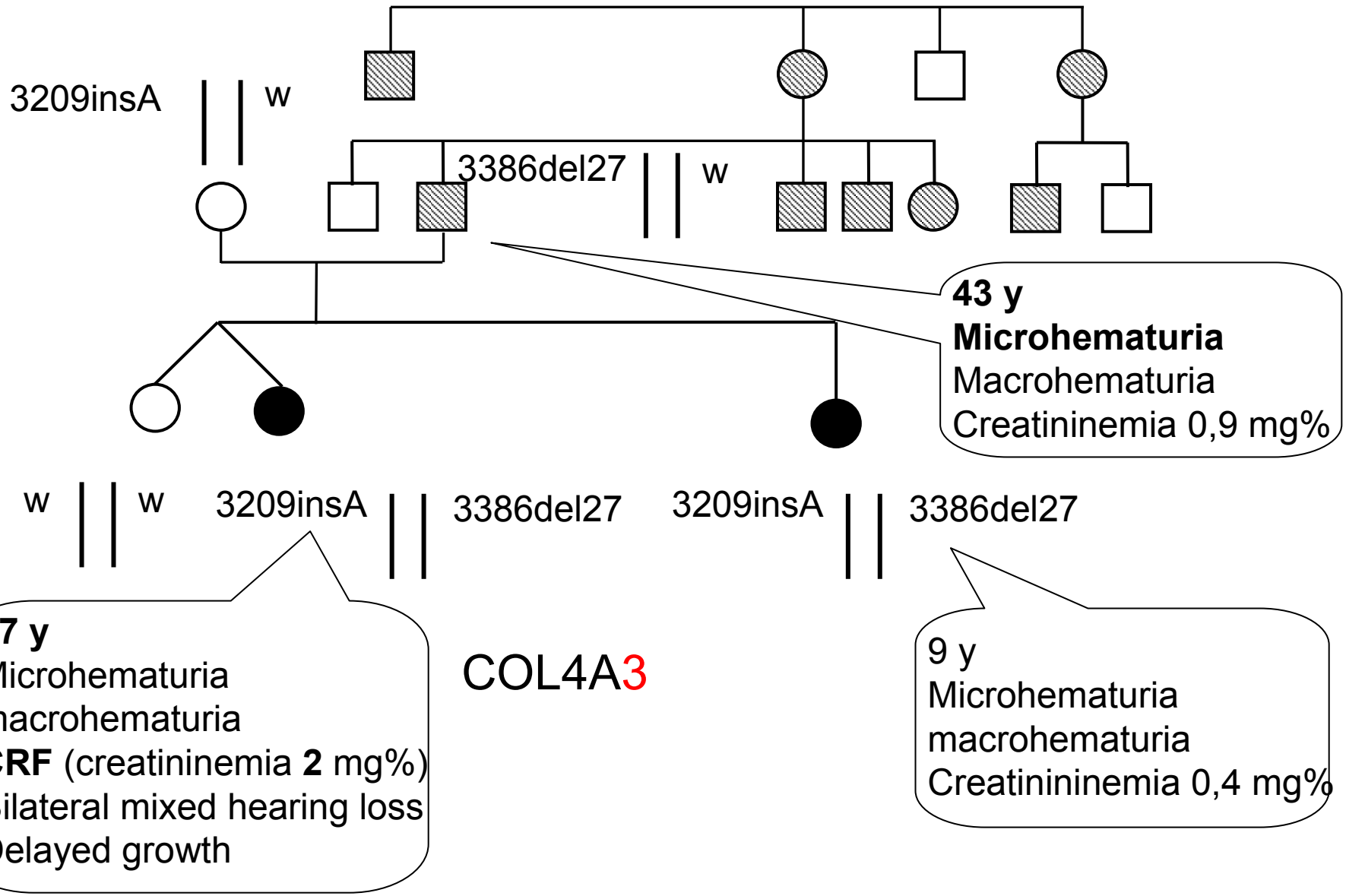
Jais JP et al, J Am SocNephrol. 2000 Apr;11(4):649-57.



Jais JP et al, J Am Soc Nephrol.2003 Oct;14(10):2603-10.

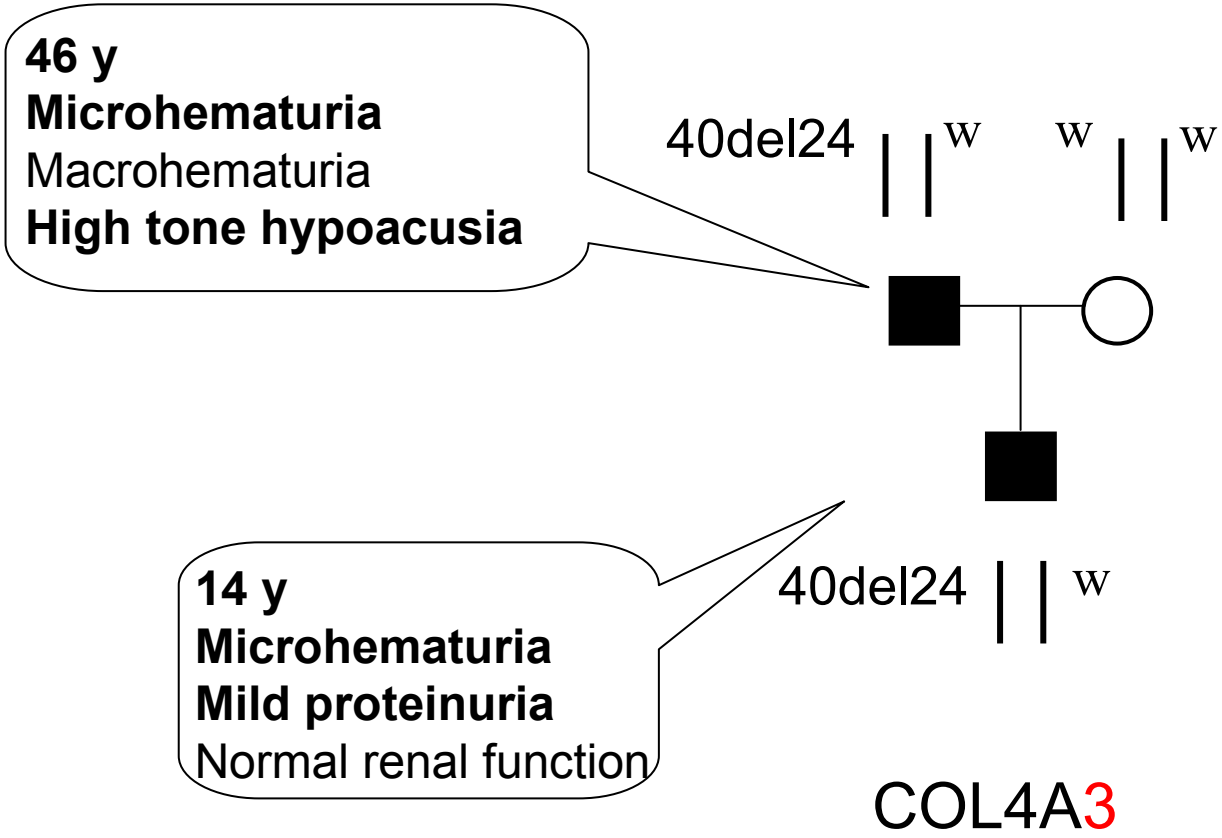


Jais JP et al, J Am Soc Nephrol.2003 Oct;14(10):2603-10.



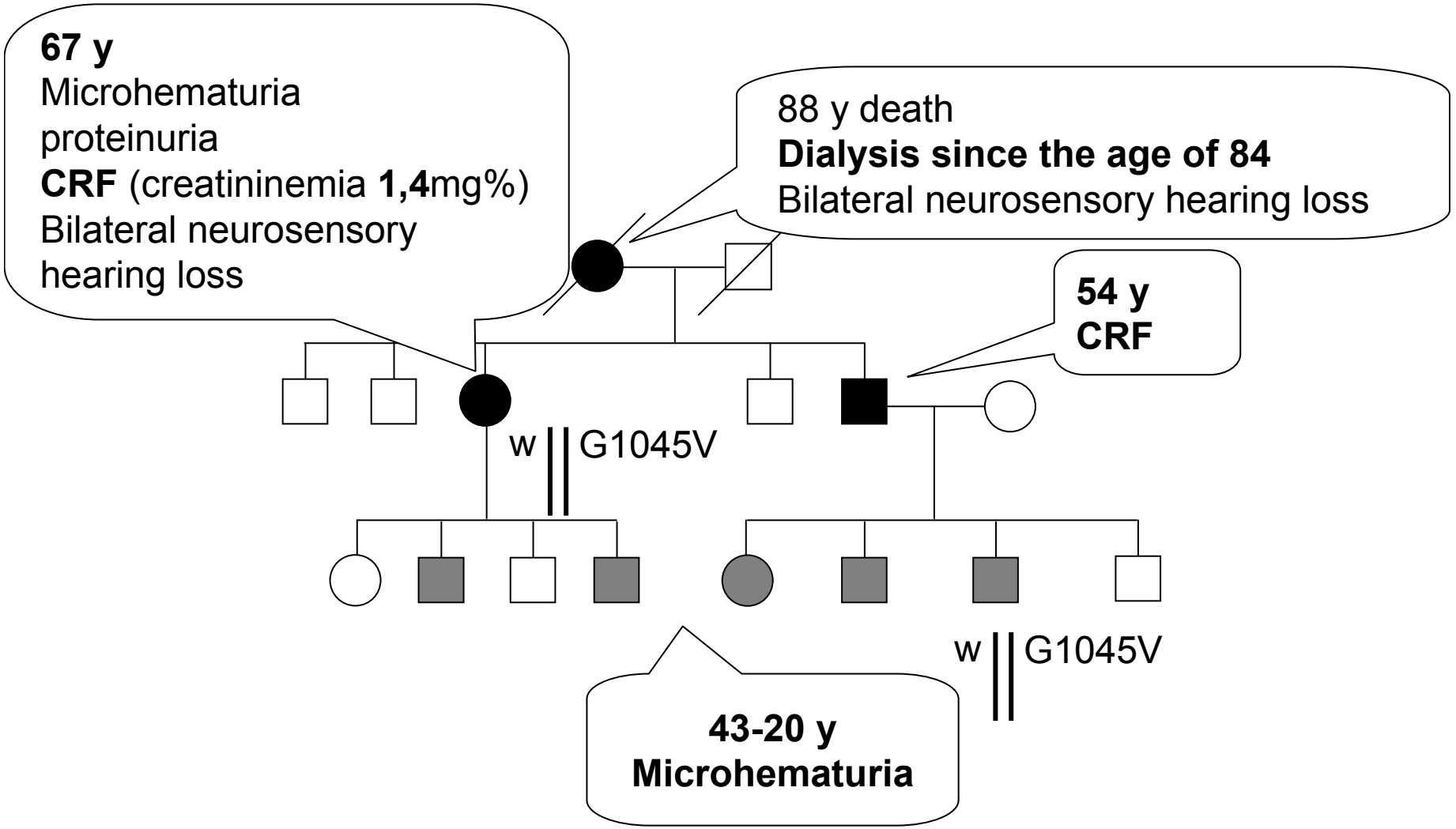
AUTOSOMAL RECESSIVE ALPORT SYNDROME

Longo I, et al. Nephrol Dial Transplant 2006;21(3):665-71.



AUTOSOMAL DOMINANT ALPORT SYNDROME

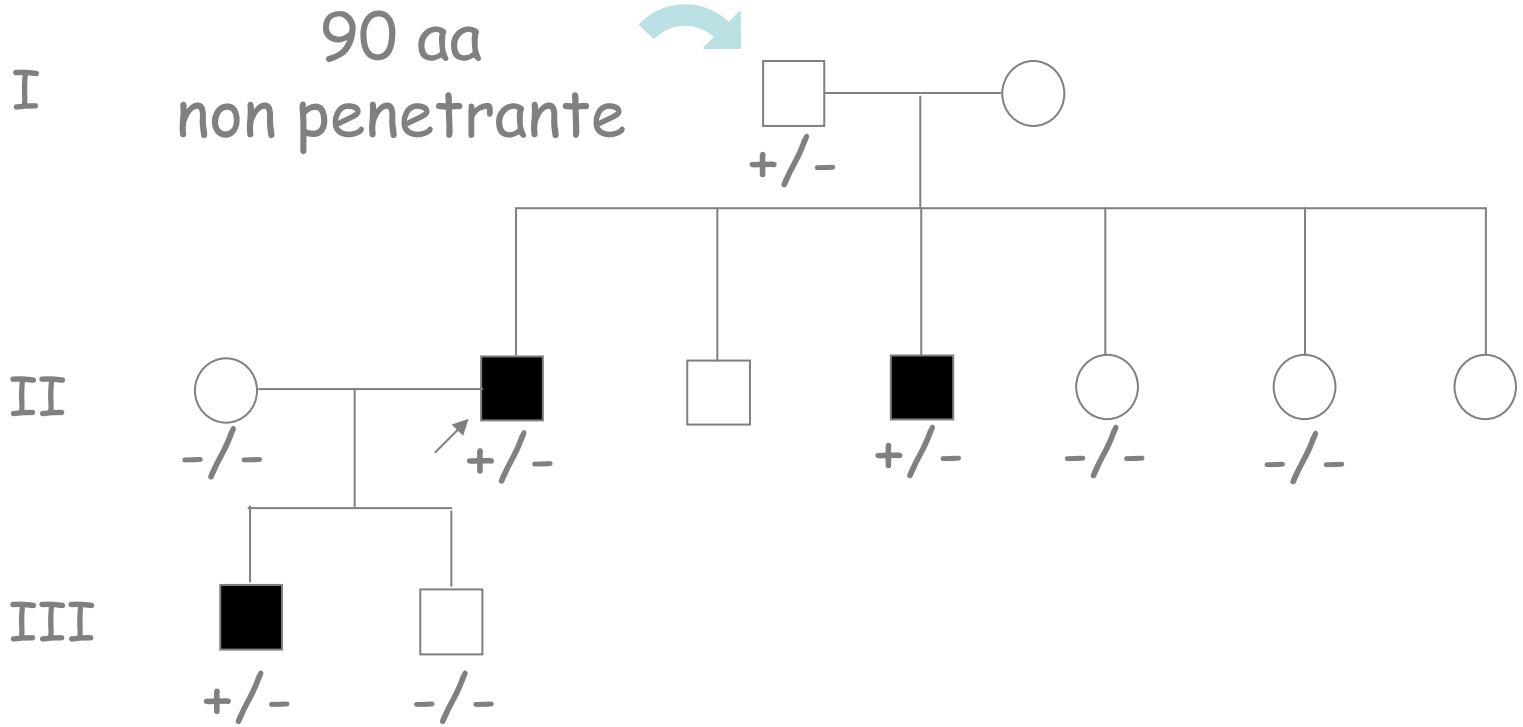
Longo I et al., Kidney Int. 2002 Jun;61(6):1947-56
Pescucci C. et al. Kidney Int. 2004;65(5):1598-603



COL4A3

AUTOSOMAL DOMINANT ALPORT SYNDROME

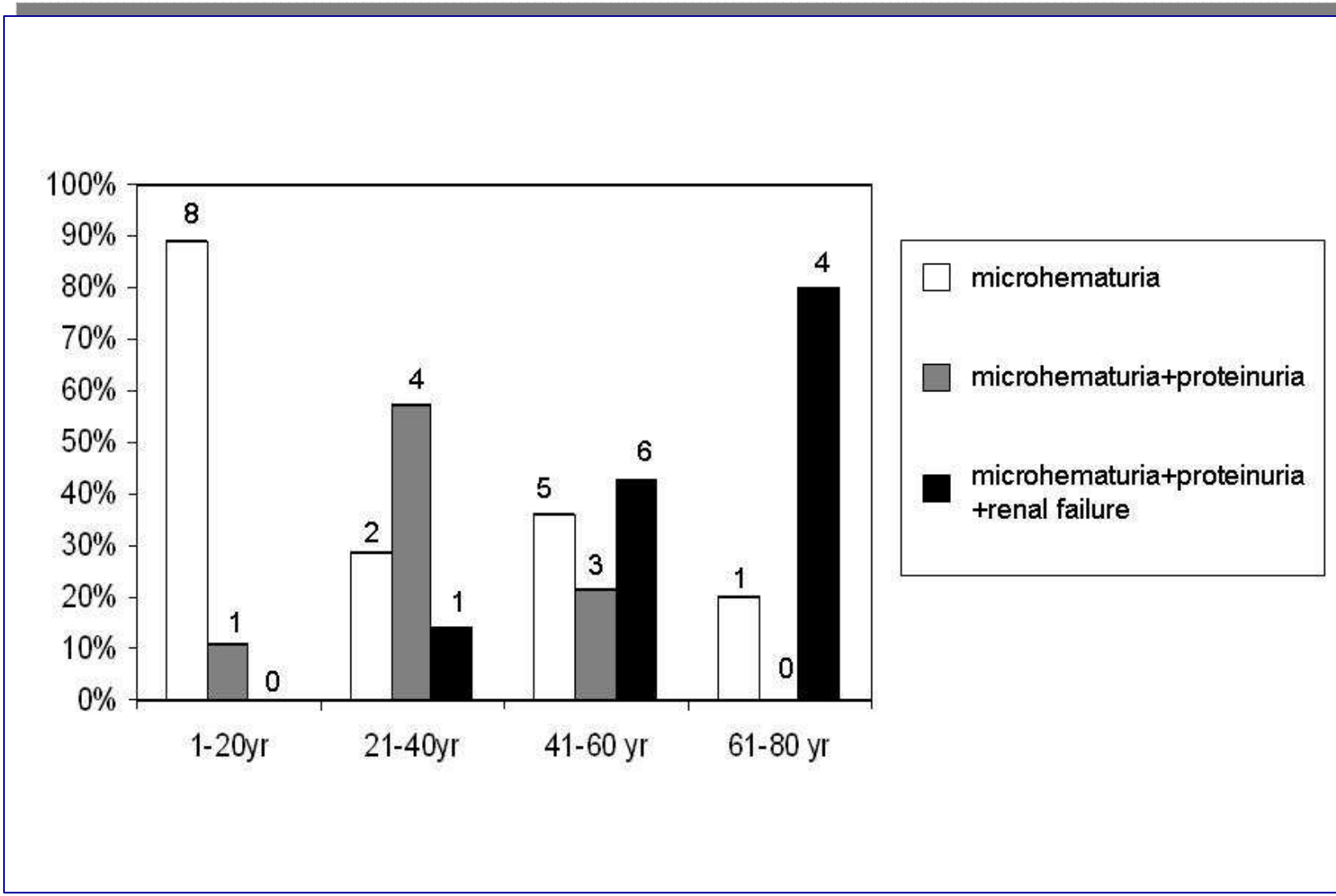
Pescucci C, et al. Kidney Int. 2004;65(5):1598-603.



p.C1634S

COL4A4

Pescucci C, et al. Kidney Int. 2004;65(5):1598-603.

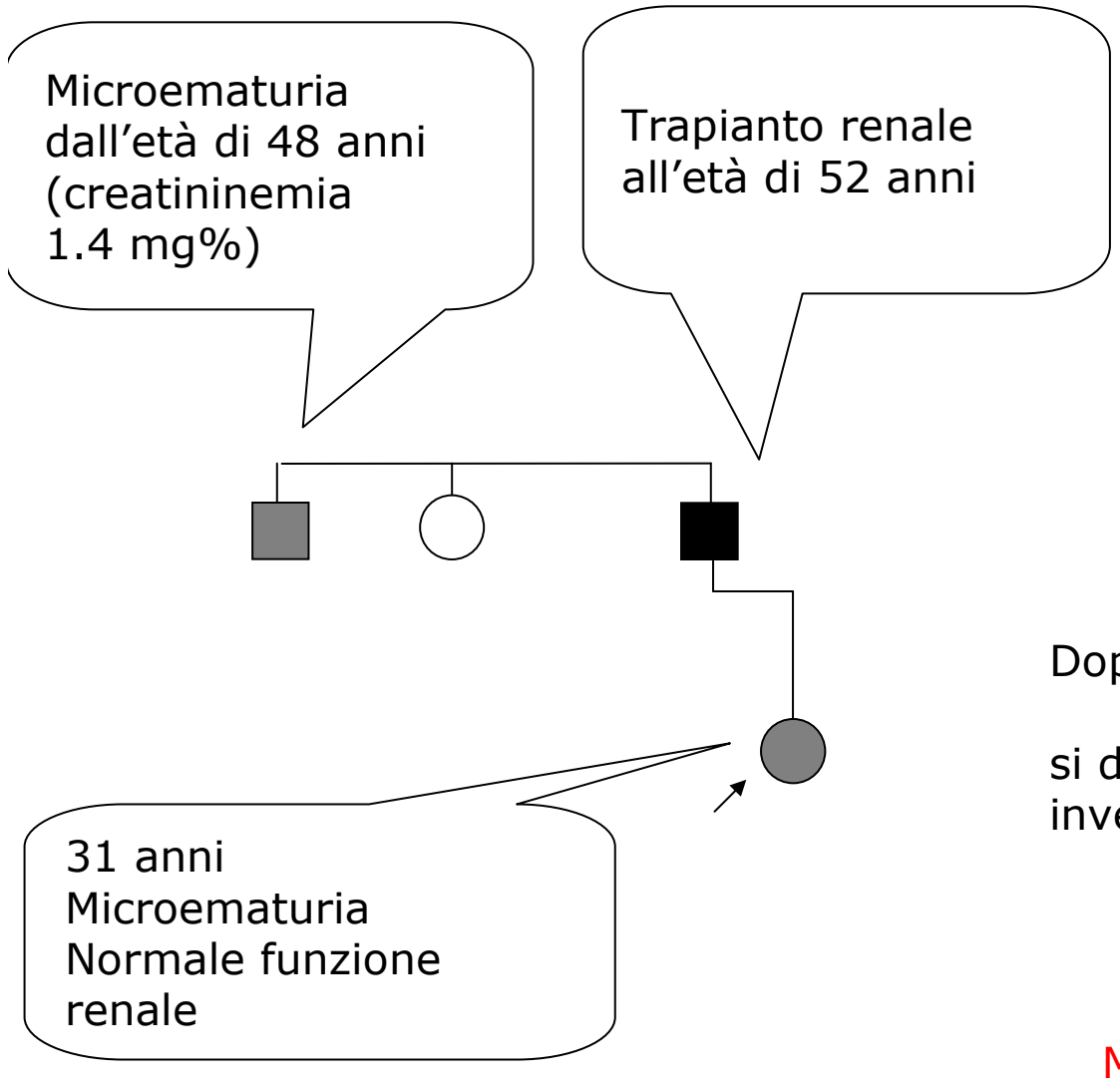


Marcocci E, et al. Nephrol Dial Transplant. 2009;24(5):1464-71.

Table 3. Clinical features of the 38 patients, in comparison with previously reported ADAS [12–15] and XLAS [5,6] patients

	Present study	ADAS literature	ADAS total	XLAS males	XLAS females
Number of patients	38	43	79	218	349
Microhaematuria	100% (38/38)	94.3% (33/35)	97.3% (71/73)	100%	95.5%
Proteinuria	50% (18/36)	41.2% (14/34)	45.7% (32/70)	95%	75.20%
Hearing loss	13.3% (4/30)	27% (10/37)	20.9% (14/67)	79%	28%
Ocular lesions	0/29	0	0	35.2%	15%
ERSD					
Onset: <31 year	0% (0/6)	0% (0/8)	0% (0/14)	76.5%	24%
Onset: 31–40 years	0% (0/6)	12.5% (1/8)	7.1% (1/14)	17.5%	31%
Onset:>40 year	100% (6/6)	87.5% (7/8)	92.8% (13/14)	6%	41%

Marcocci E, et al. Nephrol Dial Transplant. 2009;24(5):1464-71.



Arriva
dallo specialista nefrologo
con diagnosi di sindrome
di Alport X-legato e
richiesta di analisi del gene *COL4A5*

Dopo la consulenza genetica

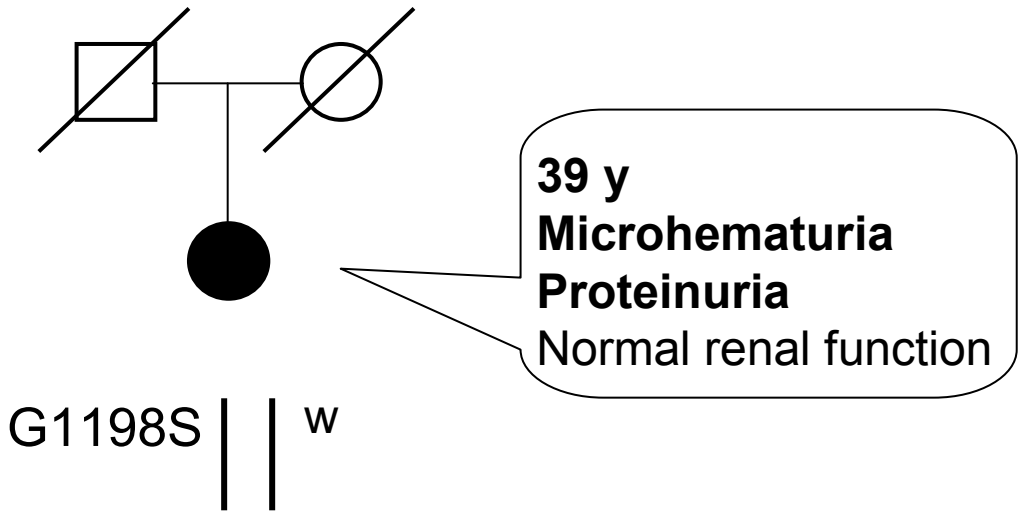
si decide di analizzare i geni *COL4A3-4*
invece del gene *COL4A5*

Mutazione nel gene *COL4A4* e

diagnosi di sindrome di Alport

autosomico dominante

family GST



COL4A3

AUTOSOMAL DOMINANT ALPORT SYNDROME, or BFH ?

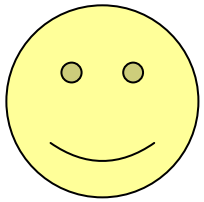
Longo I. et al, Kidney Int. 2002 Jun;61(6):1947-56.

COL4A5 hemizygous male

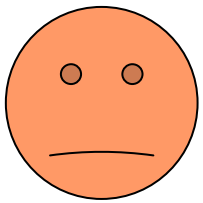
CRF

COL4A5 heterozygous female

Non sympthomatic carrier



Microhematuria



CRF

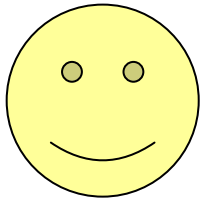
Only 15%

COL4A3/4 **homo**zygous, male/female

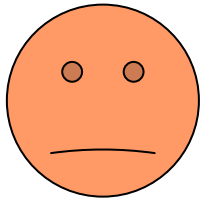
Autosomal
Recessive
Alport syndrome

COL4A3/4 **hetero**zygous, male/female

Non sympthomatic carrier



Benign
Familial
Hematuria



Autosomal
Dominant
Alport syndrome